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Asthma and Hay Fever

(Under the supervision of Richard Wiseman)

Asthma Melanodermica. Loewenthal, L. J. A., and Shapiro, S.: Arch. Dermat. **78**: 210, 1958.

A 64-year-old olive-complexioned brunette woman of mixed South African extraction, who had Portuguese, Dutch, and French ancestry, was observed by the authors during a period of hospitalization. The patient had noticed that her skin had gradually become dark during the three-month period prior to her initial bout of asthma 4 years ago. Her family history was negative for allergy. Her asthma was severe enough to require intermittent steroid or

ACTH therapy. On her initial hospital record, it had been noted that her skin was markedly pigmented. Each asthmatic attack was preceded by 3 or 4 days of gradual darkening of the skin simultaneously with a darkening of both urine and feces. Because of the change of color of her excreta, it was possible for her to forecast an attack of asthma several days before it became manifest. On prior hospital admissions, her skin was noticeably darker during the attacks of asthma and would become considerably lighter within a few days following the remission of the asthma. Since the onset of her illness there had been a marked increase in the number and size of her dermal nevi, and these lesions became darker prior to each attack. Gradually, as she developed more asthma and pigmentation, her skin remained darker, even during remissions, so that she was mistaken for a member of the Negro race.

There was no evidence of increased pigmentation of the mucous membranes of the mouth or genitals. The hair was sparse over the front of the scalp, and, except for the other changes in pigmentation described previously, her physical examination on admission to the hospital was essentially normal. Laboratory investigations disclosed normal serum iron concentrations and no evidence of porphyria. Such endocrine studies as were possible in this patient showed essentially normal adrenal and pituitary function. There were no signs of hemochromatosis, hemosiderosis, porphyria, schistosomiasis, or parasitic infestation of the lungs. Her blood smear showed an 11 per cent eosinophilia, and eosinophils were observed in her sputum on two occasions. The skin biopsy specimen showed an increase of melanin in the basal-cell layer as compared with that of a normal Caucasian brunette. Pigment was also found in the rete Malpighii, but chromatophores and hemosiderin were not seen in the dermis. The authors suggest that the increase in pigmentation may have been due either to an "increase of, or lack of opposition to, the melanocyte-stimulating hormone." Their investigations, however, failed to yield any clues regarding the nature of the relationship between the attacks of asthma and the increased cutaneous pigmentation. R. W.

Potentiating the Effect of Epinephrine With the Use of a Ganglionic Blocking Agent. Hirshleifer, I., Behr, D. J., Wigderson, A., and Jaffe, R. J.: Ann. Allergy **16**: 380, 1958.

Cannon's law of denervation states that denervation of a sympathetically innervated structure sensitizes the structure to epinephrine or epinephrine-like compounds. On the basis of this concept, a study was made to determine the effect of a ganglionic blocking agent (Methium) combined with a sympathomimetic drug in patients who had developed epinephrine resistance or in whom the epinephrine-like compounds were ineffective. A preliminary study demonstrated that the intravenous administration of tetraethyl ammonium chloride to patients in status asthmaticus provided relief which could not be obtained with epinephrine or aminophylline alone. Twenty asthmatic patients were treated in rotation with the following medications: (1) a combination of hexamethonium chloride (Methium) and Tedral; (2) Tedral alone; and (3) hexamethonium chloride (Methium) alone. Each patient was consecutively given each type of medication for approximately 4 weeks. The effect of this regime was evaluated both by clinical assessment and by timed vital capacity readings. On both scores, marked improvement in symptoms was noted when patients were receiving the combination of Methium and Tedral rather than either drug alone. When used singly, Tedral was superior to Methium. H. F.

Dermatology

(Under the supervision of Monroe Coleman)

Contact Dermatitis due to Thermo-Fax Paper. Cipollaro, A. C.: Arch. Dermat. **77**: 334, 1958.

A 41-year-old female secretary with a negative personal and family history of allergic disease developed a severe eruption involving the hands and forearms. During a six-month period, however, the lesions spread to the eyes, nares, and other areas of the face. The rash was patchy in distribution and was an erythematous, scaly, vesicular eruption. The patient had previously been treated with various remedies, including topical steroids, without appreciable relief. A diagnosis of poison ivy had been made by the physician who had first treated her. When the rash did not clear, he had performed numerous patch tests, all of which gave negative reactions. The author treated the patient with soothing topical applications along with antihistamines. Patch tests were done with Thermo-Fax paper, processed copy of Thermo-Fax paper, carbon paper, newspaper, and paper from a memo pad. Positive reactions were obtained with the Thermo-Fax paper in both the processed and unprocessed forms. On careful questioning, the patient remembered that her eruption dated back to the time her office acquired a Thermo-Fax copying machine which she operated. R. W.

Exfoliative Dermatitis as a Complication of Chloroquine (Aralen) Therapy in Rheumatoid Arthritis. Granirer, L. W.: Arch. Dermat. **77**: 722, 1958.

A 58-year-old woman who was under treatment for rheumatoid arthritis developed exfoliative dermatitis as a result of chloroquine therapy. The past history was negative for allergy or drug sensitivity, and prior to the institution of chloroquine therapy she had not received any medication for a three-month period. She was given 250 mg. of chloroquine daily for 20 days, when she developed anorexia, chills, and fever and appeared acutely ill. On physical examination, there was a scaling dermatitis over the thighs and inguinal region which later spread to involve the arms, hands, and feet. Her face, thighs, and buttocks were markedly swollen and erythematous, and a number of petechial and purpuric areas were present on her extremities. All of the laboratory studies were normal except for a positive capillary fragility test. There was no diminution of platelets, and her blood smear did not reveal an eosinophilia. She was given 5 mg. of prednisone and 4 mg. of Chlor-Trimeton 3 times daily. During the next two weeks, while she was on the above medication, her rash gradually subsided and the capillary fragility gradually returned to normal. The author believes that this patient developed an acute exfoliative dermatitis following chloroquine therapy. R. W.

Dermatitis of the Nose due to Sniff Tobacco. Shanon, J., and Tas, J.: Ann. Allergy **16**: 156, 1958.

A 72-year-old man who had sniffed tobacco for 20 to 30 years developed a dermatitis of the external nares which was at first believed to be due to arrack which was mixed with the sniff tobacco. Arrack (alcohol distilled through aniseed) is a primary irritant, and the patient was advised to refrain from adding this substance to his sniff tobacco. In spite of this precaution, the dermatitis recurred on two occasions. Forty-eight-hour patch tests with tobacco performed on the patient were positive. Patch tests performed with arrack produced a "blister."

For control purposes, 97 patients being treated for other dermatoses were patch tested with tobacco. Six of these patients reacted positively and 91 showed negative reactions. All the positive patch tests occurred in patients suffering from acute eczema and were regarded as isomorphic reactions (Koebner's phenomenon).

According to the authors, this is the first case of tobacco dermatitis ever reported in the literature. H. F.

Changes in the Histaminopexic Potency of Blood Serum in Eczemas in Adults. Sidi, E., Reinberg, A., Hincky, M., and Bourgeois-Spinasse, J.: Presse méd. **66**: 343, 1958.

The absence or reduction of the histaminopexic potency of blood serum is characteristic of the allergic terrain. This serologic state was found in 68 of 75 cases of atopic dermatitis and in 39 of 47 patients with contact dermatitis. It therefore could not serve as a differential test. There was an increase of the histaminopexic potency as the patients improved clinically. I. G.

Sensitivity to Fluorescent (Blue-Green) Light. Lamb, J. H., Jones, P. E., Rebell, G., and Alston, H. D.: Arch. Dermat. **77**: 519, 1958.

The subject of light sensitivity is reviewed and a case report is presented. The patient, a 45-year-old female schoolteacher, complained of a severe, recurrent erythema on the exposed parts of the body. Prior to the development of her rash, she had been in good health except for some mild menopausal symptoms. During a long motor trip three months previously she first noticed burning and redness of her face and neck. During subsequent weeks she noticed an aggravation of her rash after walking outdoors in natural sunlight. The erythema usually subsided shortly after going indoors, but she found that each day the redness and burning appeared to last a little longer. She also noticed that following a 30-minute stay in her bathroom she had a flare-up of symptoms. The lighting fixtures in the bathroom were fluorescent tubes which were placed on each side of the medicine cabinet. When she reported this response, her condition was diagnosed as a blue-light sensitivity, and she was treated with hydroxychloroquine, 400 mg. daily, and a light-screening ointment (A-Fil containing methyl anthranalate). When she failed to improve, she was given chloroquine, another antimalarial, but this drug produced no beneficial effects and had to be discontinued because of undesirable side effects. She continued to have a deep erythema on the skin of her arms and legs (below the knees), with sharp lines of demarcation on the arms where her skin was protected from sunlight by her coat.

Exposure to 5-watt fluorescent lights at 6 inches produced immediate erythematous urticarial responses within 15 minutes. Window glass of 2 mm. thickness was found to diminish the skin response to fluorescent light, and frosted glass of equal thickness produced even more blocking of the sensitivity response. When a test was made with a 500-watt projection type incandescent light with a known range of 4,000 to 7,000 A at 19 inches from the skin, there was an immediate whealing reaction after 8 minutes. The skin was kept cool by the use of fans so that there could be no question that the response was strictly related to the light exposure and not to the heat of the light bulb. Skol (a preparation containing aminobenzoic acid) was placed over an area of skin which was subsequently exposed to both the fluorescent and the incandescent lights. It failed to prevent the occurrence of the erythematous reaction. Skol is said to have an absorption spectrum ranging

from 2,500 A to 3,200 A. Passive transfer studies were attempted, but both the fluorescent light and the projection incandescent light failed to produce positive reactions on substitutes sensitized with the patient's serum. The patient was then treated with testosterone parenterally at weekly intervals and was instructed to avoid exposure to fluorescent light. After four months of therapy her skin became tanned and all tests to blue light were negative. The rationale of testosterone therapy was not discussed. Because fluorescent lighting is so widely used, "it behooves the dermatologist to be cognizant of its photosensitizing action in erythema solare, subacute lupus erythematosus, and polymorphic light eruptions that fail to respond to the antimalarials." R. W.

Dynamics of Autosensitization Dermatitis. Young, A. W., Jr.: Arch. Dermat. **77**: 495, 1958.

Sixty patients (33 women and 27 men) suffering from a generalized autogenous eczema were studied. They ranged in age from 1 to 80 years, the average age being 48 years. Over one-half the patients in the series had atopic backgrounds. The lesions consisted of recurrent persistent rashes of long standing and had been variously diagnosed as nummular eczema, stasis or neurostatic dermatitis, lichen simplex chronicus, contact dermatitis, dry eczema of hands or legs, axillary dermatitis, scrotal eczema, seborrheic-like dermatitis, senile pruritus, ear canal eczema, intertrigo, and eczema of undetermined etiology. The dermatitis was acute, weeping, vesicular, and crusted prior to the onset of the generalized autoeczematization, with the spread usually following within a week after the exacerbation of the rash. The spread of the rash followed a changing pattern, the initial lesion being a minute vesicle on an erythematous base in close proximity to the original dermatitis. At first the lesions involved flexural surfaces typical of an atopic reaction and occurred often in areas which had previously undergone an atopic response. The expanding lesions also had a predilection for residual scars from herpes zoster, thermal burns, and donor areas for skin grafts. Rarely did the extensor areas show the first signs of the spreading eruption, and this occurred only in cases where there were pre-existing changes, such as senile skin or xeroderma of long duration. As the rash spread, the primary lesions tended to form orbicular patches which became edematous, raised, crusted, and often secondarily infected. The individual lesions appeared indistinguishable from nummular eczema. Occasionally the rash could be controlled at this point and prevented from progressing to a more serious condition. When the condition was not controlled, the eczematous patches became enlarged and new lesions appeared and spread to involve large areas of skin. At times the condition was so severe that it resembled exfoliative dermatitis.

In the course of autoeczematization, hemorrhagic vesicobullous or even pustular lesions frequently occurred on the palms and soles. An ill-defined urticarial erythematous reaction was occasionally seen around the eyelids. Resolution was detected by central clearing of the lesions, usually followed by pigmentation within the orbicular area with the eventual appearance of small islands of normal tissue within the area. Many of the patients related underlying tensions and emotional difficulties to the onset of the generalized disorder or exacerbation of the primary local dermatitis. Histologic studies were made on 11 patients. A single pathologic process was found throughout, varying degrees of intensity being observed in each patient. The basic response was found to be a simple cellular focal vascular reaction involving

both the dermis and the epidermis. The vessels of the middle and upper cutis were dilated, and their walls were thickened. Perivascular infiltration, consisting of small round and wandering connective tissue cells, and interstitial edema were present. "Variations occurred with respect to numbers of eosinophils within the infiltration, the presence of blood cellular elements in the vessel lumen, and the amount of interstitial edema. . . ."

Generalized autogenous eczema is described by the author as a disorder which progresses through some or all of the following stages: vesicular, organizing, confluent (spreading), multiform (diffuse), and resolving (generalized). There is a close clinical relationship between the individual stages of generalized autogenous eczema and cases of neurodermatitis, nummular eczema, exudative discoid and lichenoid chronic dermatosis, and dermatitis herpetiformis. "This relationship is further confirmed by the microscopic process." An allergic background and/or an emotional disturbance are commonly associated with these dermatoses. These observations would seem to indicate that all of the aforementioned dermatoses and generalized autogenous eczema belong to the same group of diseases. R. W.

Dermatitis of the Fingers From Rosary Beads. Rubin, A.: Arch. Dermat. **77**: 732, 1958.

A 36-year-old woman with a rash of about two months' duration on the index finger and thumb of the right hand was observed. The rash was well marginated and involved the terminal portion of the right index finger and the tip of the right thumb. Within a few weeks she developed a similar rash on the same areas of the left hand. The involved areas itched, burned, and showed the typical clinical picture of contact dermatitis. Wearing rubber gloves to avoid contact with soap and water failed to improve the lesions, and topical medications afforded little relief. When the patient discontinued using her rosary beads, the rash quickly cleared. On careful questioning, it was learned that her husband had recently given her a rosary made of olive wood and imported from Italy. For years the patient had handled glass rosary beads and had never had any difficulty. It was learned from a dealer in religious items that the wood in these rosaries is lacquered with a plastic material which was apparently the excitant of the contact dermatitis in this case. Within 48 hours after discontinuing exposure to the wooden beads the patient's fingers showed marked improvement, and by the end of a week the rash had entirely cleared. R. W.

Cheilitis—Unusual Manifestation Due to Solar Sensitivity. Cobin, I. M.: Arch. Dermat. **78**: 91, 1958.

The author describes the case of a 43-year-old woman with a history of severe cheilitis of several months' duration. There was marked peeling of the lips, together with fissures at the corners of the mouth. The condition was characterized by constant exacerbations and remissions and never completely cleared. Therapy at first consisted of the administration of vitamins and the application of hydrocortisone and Mycostatin ointments without beneficial effects. She was also treated for a mild scalp seborrhea. Changing of her toothpaste failed to improve the condition, and patch tests with lipstick and the filter from the cigarettes which she smoked were negative. During the course of observation she mentioned that she had been taking a nerve pill, which proved to be chlorpromazine (Thorazine). She was given a different sedative, and concomitantly there was a definite improvement in her lips.

Patch tests were performed with chlorpromazine, and within 48 hours a large blister appeared at the site of the tests. Several weeks later she again chewed a chlorpromazine tablet and the condition on her lips promptly recurred following exposure to sunlight. The author suggests that this patient had a localized solar sensitivity due to chlorpromazine sensitivity which produced the cheilitis. R. W.

Experimental Evidence for an Allergic Basis for Granuloma Formation in Man. Shelley, W. B., and Hurley, H. J.: Nature **180**: 1060, 1957.

Ten healthy subjects were each given 4 intracutaneous and 4 subcutaneous injections of 0.02 ml. of a 1.0 per cent aqueous solution of sodium zirconium lactate. In all a small, firm, fibrous papule developed at the sites of the intracutaneous injection but not at the sites of the subcutaneous injections. Biopsy of the papules revealed a noninflammatory fibrous mass, histologically resembling a scar. At the end of six months one of the subjects suddenly developed an enlarging mass at each site of the eight previous injections. Biopsy specimens disclosed a classical epithelioid granuloma in both the dermal and the subcutaneous injection sites, and zirconium was present in a concentration of 10^{-5}. An intracutaneous injection of 0.02 ml. of a dilution of 10^{-5} of sodium zirconium lactate in this patient resulted in a clinical and histologic response within seven days in the form of papules with epithelioid cells which persisted for months.

Six patients who developed axillary granulomas following the use of zirconium deodorants were studied. Each developed delayed local granulomas at the sites of injections of sodium zirconium lactate. There was no response to patch tests with zirconium.

The suspected allergic nature of these granulomas was based on the facts that (1) the state of hypersensitivity was acquired, (2) the granuloma reaction was specifically elicited only by zirconium, and (3) extremely high dilutions of the zirconium were capable of producing the granulomatous response. I. G.

Swimmers' Itch in New Jersey. Stauber, L. A.: J. Parasitol. **44**: 108, 1958.

Dermatitis-producing cercariae were found in a swimming pond constructed from a dammed portion of a spring-fed brook in Summit, New Jersey, and also in tidal flats of the Bay Shore of Cape May, New Jersey. Human beings swimming in both these sites experienced itching dermatitis. Children previously unexposed to the parasites developed less itching and evidenced slower-developing lesions than adults who had swum in infested waters previously and presumably had become sensitized. E. K.

Clinical and Pathological Findings in the Skin in Anaphylactoid Purpura (Allergic Angiitis). Winkelmann, R. K.: Proc. Staff Meet., Mayo Clin. **33**: 277, 1958.

Anaphylactoid purpura is one of a group of diseases characterized by cutaneous or mucosal hemorrhages due to dermal or submucosal vasculitis. These hemorrhages may be gradual or acute, episodic or continuous. They often are associated with maculopapular, urticarial, or vesicular lesions which may proceed to the formation of bullae or to necrosis and ulceration. In these conditions, blood coagulation factors are normal, the sedimentation rate is elevated, a mild eosinophilia is present, and leukocyte counts are only

slightly increased, even in the presence of a high fever. Arthritic, gastrointestinal, renal, and other symptoms may occur, depending on the location of the hemorrhages.

The following terms have been used in association with various forms of anaphylactoid purpura (allergic angiitis): purpura rheumatica, Schönlein-Henoch syndrome, necrotizing angiitis, hypersensitivity periarteritis nodosa, nodular allergia of Gougerot, allergic microbid, and erythema elevatum diutinum. The following diseases are also related: systemic angiitis, lethal midline granuloma of the nasopharynx, allergic granulomatosis, Wegner's granulomatosis, temporal arteritis, and periarteritis nodosa. The condition is frequently associated with the use of drugs, such as sulfonamides, antibiotics, anticonvulsants, or barbiturates. In one case, Benadryl has been implicated. In several cases, exposure to insecticides and weed killers appeared causative. Other instances have been associated with foods, such as fish and lamb, and it is suspected that injections of serum or bacterial allergens or natural streptococcic infections may elicit lesions of this kind.

From the standpoint of pathology, the disease may be described as an acute or chronic necrotic reaction in the vascular wall with granulomatous degeneration of the surrounding tissues and extravasation of blood. Biopsy of the skin is important in establishing the diagnosis.

Five case reports are presented to demonstrate the relationships between the various clinical manifestations and their underlying pathology. The patients, three male and two female, ranged in age from 17 to 75. Hemorrhage took the forms of purpura, epistaxis, hematuria, hematemesis, and melena. In one case, however, which was described pathologically as a periphlebitis, there was no hemorrhage. Other skin lesions included nodules, papules, maculopapules, ulcers, bullae, erythematous plaques, and urticaria. Symptoms varied in each case with location of the disease process, but they commonly included arthralgia, albuminuria (with hematuria), and fever. One case was associated with exposure to the weed killer 2,4-D and one with injections of bacterial allergens for chronic sinusitis. In the other three cases no agent was implicated. Three cases were treated with steroids; the other two were treated symptomatically. Steroid therapy is strongly indicated in advanced cases. There was one mortality; at necropsy, the diagnosis of periarteritis nodosa was made. D. GITLIN

Miscellaneous Allergies

(Under the supervision of Eugene Walzer)

Agranulocytosis Following Use of Nartate (Dipyrone). Borelli, L. R.: New York J. Med. **58**: 3179, 1958.

A case of agranulocytosis following the use of Nartate, which had been prescribed as an analgesic for relief of intercostal pain, is reported. The patient, a 66-year-old woman, developed an acute exudative tonsillitis and pharyngitis, accompanied by a temperature of 106° F. She gave a previous history of sensitivity to penicillin. Treatment with Chloromycetin was begun immediately, and the patient was hospitalized. The initial blood count revealed the following: 4,170,000 red blood cells, 74 per cent hemoglobin, and 200 white blood cells with a differential of 100 per cent lymphocytes. Investigation revealed that the patient had taken 32 Nartate tablets over a five-day period 4 weeks prior to the present illness. She was treated with steroids,

calcium leucovorin, pentonucleotides, blood transfusions, Reticulogen, and Ilotycin. Bone marrow studies performed 4 days following the onset of illness revealed an absence of the more mature forms, indicating a maturation arrest of the granulocyte series at the level of young myelocytes. Plasma cells and megakaryocytes were somewhat increased, but the megakaryocytes appeared to be producing platelets, even though the peripheral platelet count was only 60,000. A second bone marrow study done 4 days after the first one showed marked improvement. There was a considerable increase in the number of mature granulocytes, and there was no longer any evidence of maturation arrest. During the next 8 weeks the patients made a gradual recovery while on continuous medication. During convalescence, she developed onychomadesis of the nails as well as two sterile abscesses which required incision and drainage. The author emphasizes the fact that toxic damage following Nartate medication may not be manifest until several weeks following cessation of the drug. R. W.

Focal Hepatitis, Fever and Skin Rash Following Therapy With Sulfamethoxypyridazine, a Long-Acting Sulfonamide. Tisdale, W. A.: New England J. Med. **258**: 687, 1958.

A 68-year-old Negro received sulfisoxazole, 4.0 Gm. a day, for five days prior to a suprapubic prostatectomy. Following surgery, he received procaine penicillin and streptomycin for 10 days. On discharge, he was asymptomatic. A daily dose of 4.0 Gm. of sulfisoxazole was continued. On a subsequent visit to the outpatient department, the patient was given sulfamethoxypyridazine, 1.0 Gm. orally each day for 37 days, and nitrofurantoin, 300 mg. orally for about two weeks. After completing the course of sulfamethoxypyridazine, he experienced a severe, generalized itching and noted a rapidly progressive maculopapular eruption over the skin of the arms, legs, and trunk. Two days later there was "dark red" urine and a rise in temperature to 102° F. There was no history of previous liver disease. Physical examination revealed an acutely ill man with a diffuse, confluent, erythematous papular rash, scattered petechial lesions of the buccal mucous membranes, scleral icterus, and a slightly enlarged, soft, tender liver. Urinalysis revealed a negative albumin test and a two-plus test for bilirubin. A mild leukopenia was present. Microscopic examination of a liver biopsy specimen revealed a disseminated exudative process that involved the parenchyma, portal triads, and venous radicles. The intralobular lesions consisted of large collections of mononuclear and occasional polymorphonuclear cells scattered throughout the sinusoids and within parenchymal plates, where isolated cells either had dropped off or were undergoing necrosis. There was focal swelling and proliferation of adjacent Kupffer cells. Many of the portal zones contained large numbers of mononuclear cells, surrounding both biliary radicles and vessels. On bed rest, high fluid intake, local skin therapy, and the oral administration of prednisone, chloramphenicol, and streptomycin, the patient made a rather uneventful recovery. A repeat liver biopsy several weeks after admission to the hospital demonstrated complete disappearance of the focal inflammatory lesions. Intracutaneous tests, using 0.05 ml. aliquots of serum from a patient receiving sulfamethoxypyridazine and from another patient who had received 300 mg. of nitrofurantoin, were carried out. In all cases, the erythema and induration induced by the drug-containing serum did not exceed that produced by the control serum. Patch tests with sulfamethoxypyridazine and nitrofurantoin were also negative. The clinical manifestations, laboratory features, and pathologic lesions of the drug-induced "hypersensitivity" hepatitis are described and discussed. E. W.

Anaphylaxis

(Under the supervision of Harold Friedman)

Altered Reactivity to Epinephrine in the Hypersensitive Rabbit. Gatling, R. R.: J. Exper. Med. **108**: 441, 1958.

Horse-serum-sensitized rabbits were given a challenge dose of from 1 to 5 ml. of horse serum intravenously, and at the same time epinephrine or norepinephrine was injected intracutaneously in varying amounts. At the epinephrine site of a full-blown reaction, the initial blanching was followed 14 hours later by a dark blue nonelevated lesion measuring approximately 3 cm. across.

The intensity and diameter of the epinephrine lesion were found to be directly proportional to the intensity of the Arthus reaction, except that when the horse-serum injection induced anaphylactic shock the epinephrine lesion did not develop. The amount of antigen injected (circulating antigen) had relatively little effect on the epinephrine lesion. When the intravenous antigen challenge dose was omitted, the epinephrine lesion did not occur. Epinephrine in doses at or below 20 mcg. did not elicit reactions; 100 mcg. doses gave optimal reactions. The administration of epinephrine intracutaneously at time intervals of up to 4 hours after serum challenge resulted in local reactions. At a six-hour interval the reaction appeared to be fading out. It was felt that "in some way, the circulating antigen was utilized in producing the epinephrine lesion." Heparin administration counteracted the appearance of the epinephrine lesion, but chlorpromazine had no effect. Heparin counteracted the Arthus reaction but had no effect on the epinephrine reaction in animals prepared with endotoxin. Chlorpromazine counteracted epinephrine lesions in endotoxin-prepared rabbits. Ephedrine injected intracutaneously failed to elicit epinephrine-like reactions in the hypersensitive rabbits with circulating antigen, indicating that "more than simple vasoconstriction is involved in initiating the epinephrine lesion." The addition of epinephrine or norepinephrine to horse serum injected intracutaneously to elicit Arthus reactions changed the appearance of the lesion to the rimmed one characteristic of the epinephrine reaction. It is suggested that the epinephrine lesion may be identified with the Arthus reaction. E. K.

Antibody Production by Guinea Pig Cells Demonstrated by the Passive Cutaneous Anaphylaxis Reaction. Rosenberg, L. T., Chandler, M. H., Gordon, A. S., and Fischel, E. E.: J. Immunol. **81**: 136, 1958.

Passive cutaneous anaphylaxis was used to detect antibody production by cells transferred from immunized guinea pigs and implanted intracutaneously into normal guinea pigs. The local antibody production was detected by inducing the PCA reaction with excess antigen and a dye indicator, T-1824, injected intravenously.

Albino guinea pigs served as cell donors and recipients. The antigens most frequently used were pooled human serum and 4 times recrystallized hen egg albumin (Ea). After a single intravenous injection of antigen into the donor, cell suspensions were made from spleen, liver, bone marrow, lymph nodes, and thymus removed from one to twenty-one days later. Hanks' balanced salt solution (BSS) was used for triple washing and for suspensions of the cells. From 0.1 to 0.3 ml. of suspension was injected intracutaneously in the recipients. The intravenous challenge with antigen and dye was made

at intervals of a few hours to seven days. Fifteen minutes after the challenge the recipients were sacrificed, their skins were reflected, and the cell sites were examined for excessive dye leakage. Many control materials, such as heated and frozen donor cells, supernates of the first cell wash, donor's serum, and normal cells, were used.

Disrupted cells, heated or frozen and thawed cells always failed to sensitize recipient sites. Antibody appeared in the donor's serum about seven days after immunization but was effectively removed from the transferred cells by three washes.

One million of the immunized animal spleen cells were usually sufficient to sensitize recipient cutaneous sites for PCA reactions. With cells obtained within the first week following immunization, sensitization of PCA sites developed within one to three days. Cells taken at seven days tended to sensitize sites more rapidly than those taken earlier in the first week. Pre-formed antibodies in donor's serum produced active sites within two hours after injection. Site reactivity following cell injections was usually gone by the sixth day. Bone marrow, lymph node, liver, and circulating white blood cells did not sensitize skin sites of the recipient. Thymus cells occasionally gave positive results. B. S.

Anaphylaxis and the Nervous System. Part IV. Szentivanyi, A., and Szekely, J.: Ann. Allergy **16**: 389, 1958.

It has been demonstrated that bilateral focal lesions of the tuberal region of the hypothalamus produced by the Horsley-Clarke stereotaxic apparatus results in the inhibition of anaphylactic shock and of antibody production. It was also noted that the nonspecific phase of anaphylactic shock was modified by this operative procedure. It was further demonstrated that this procedure did not influence antigen-antibody union or the liberation of tissue material during shock. On the basis of this latter observation, the histamine resistance of the tuberal-injured animal was next investigated. It was first noted that the tuberal-injured animal had a less pronounced fall in temperature following histamine injections than did normal animals. A second series of tuberal-injured guinea pigs, along with appropriate controls, was given histamine in amounts that were approximately one and one-half times the 100 per cent lethal dose. Characteristic symptoms of histamine shock developed equally in the tuberal-injured and in the control animals. The control animals died within an average of 10 to 15 minutes after the histamine injection. Thirty-four per cent of the tuberal-injured animals survived the shocking dose. Six weeks after the first shock the surviving animals were given the same dose of histamine and all died with the exception of one animal which died during a third histamine shock induced three weeks later. Another group of 43 tuberal-injured animals and 27 control animals was given histamine injections seven weeks after the operation. The animals in both groups died within the same period of time, thus indicating that the histamine resistance of tuberal-injured animals was of a transitory nature.
H. F.

Quantification of Anaphylaxis in Mice. Harris, W. E., and Fulton, J. D.: Proc. Soc. Exper. Biol. & Med. **97**: 14, 1958.

Two different sensitizing-challenge procedures were utilized to demonstrate the relationship between the degree of hemoconcentration in the mouse

and the concentration of the challenge antigen. With the first method, female Swiss-Webster mice were sensitized by means of two intraperitoneal injections of alum-precipitated bovine albumin with *Hemophilus pertussis* vaccine. Eight days later rapid intravenous challenge was accomplished by the instillation into the tail vein of graded quantities of albumin and pertussis vaccine cells. The second method involved the subcutaneous introduction of a bovine albumin—Freund's adjuvant mixture, followed in 21 days by the intravenous administration of varying concentrations of bovine albumin in saline. The hematocrit levels of blood samples obtained at specified intervals were used to calculate the percentage of hematocrit change. Appropriate control procedures were run with each experiment. Statistical analysis of the data obtained from both sensitizing-challenge procedures revealed that the hematocrit change and mortality are positively related to the challenge antigen concentration. Percentage hematocrit change plotted against log dose antigen concentration produced a sigmoidal curve, a portion of which indicated an almost linear relationship. Control animals showed no hematocrit change and insignificant four-hour postchallenge mortality rates. Calculation of hematocrit change is suggested for quantitative comparisons of mouse anaphylaxis. H. STRYKER

Otorhinology and Ophthalmology

(Under the supervision of Hilda Stryker)

Inhalant Allergy in Infants. Wood, B. J., and Walker, D. H.: Ann. Allergy **16**: 451, 1958.

The early recognition and proper management of allergic respiratory conditions in children can prevent eventual chronic disabilities. House dust is one of the most important causes of allergic disturbances of the respiratory tract, even in the first two years of life. A group of 150 patients, all under 2 years of age, whose upper respiratory symptoms had failed to respond to the usual therapy were started on desensitization with house dust extract plus pollen extract and respiratory vaccine when indicated. The diagnosis of inhalant allergy in these cases was based on the following findings: (1) history of repeated respiratory disturbances; (2) positive family history; (3) positive skin reactions; (4) physical signs presenting evidence of vasomotor rhinitis; (5) eosinophils in the nasal smear; and (6) appropriate x-ray and laboratory studies. Skin tests yielded a positive reaction to house dust in 62 per cent, to pollens and other inhalants in 32 per cent, and to foods in 56 per cent of the patients in this series. Treatment was begun with dilutions of Endo dust ranging from 1:100,000,000 to 1:100,000. Initial doses stronger than 1:100,000 consistently aggravated symptoms. Treatment was administered intracutaneously at four- to seven-day intervals in increments of 0.03 c.c. up to a maximum of 0.3 c.c. of the most dilute solution. A similar series was then given from the next concentration of dust extract, the entire plan of therapy being based upon the individual's response. The dosage was increased until symptoms were completely controlled and then was maintained at that level. The interval between injections was gradually lengthened. The average duration of treatment was one year. Sixty-two per cent of the group experienced excellent results, 30 per cent had good results, and 8 per cent were unimproved. H. F.

Pharmacology, Physiology, and Pathology

(Under the supervision of Bernard Siegel)

The Local Response of Tissue Mast Cells to Antigen in Sensitized Mice. Carter, P. B., Higginbotham, R. D., and Dougherty, T. F.: J. Immunol. **79**: 259, 1957.

Horse-serum-sensitized mice and nonsensitized controls were challenged 3 to 4 weeks after sensitization with either the homologous antigen or calf serum. The challenging dose of antigen was administered into an air pouch produced on the dorsal surface of the animal by a previous subcutaneous injection of air. At varying intervals thereafter, the bubble of connective tissue was dissected free from the surrounding tissues, spread on a glass slide, and stained. Counts were then made of the number of degranulated mast cells among 200 mast cells of the loose connective tissue of mice in the various groups. Among the sensitized mice challenged with homologous antigen, an average of 155 degranulated mast cells was found within 5 minutes after the challenging injection. Among the sensitized animals challenged with heterologous antigen and the nonsensitized animals challenged with horse serum, an average of 27 and 36 degranulated mast cells respectively was found within 5 minutes after the challenge.

Qualitative studies revealed that within 5 minutes after the local injection of homologous antigen into a sensitized animal an explosive degranulation of mast cells occurred. The granules spread widely into the ground substance and exhibited a reddish metachromatic reaction to the stain. Under other conditions the granules take on a purplish to blue color. The red reaction suggests the presence of free heparin, whereas the purple to blue color suggests the presence of heparin in combination with other substances. Thus, it is inferred that free heparin is liberated from the mast cell granules in a local hypersensitivity reaction.

Studies done at longer intervals following the challenging injection revealed that the surrounding fibroblasts had ingested many of the shed granules within one hour. These granules differed from those found in normal mast cells in that they varied in their size and in their affinity for the stain. Within one to four hours there was a reappearance of metachromatically granulated cells. Twenty-four hours later the extracellular granular material was no longer visible. In 2 or 3 days, the metachromatic substances appeared as discrete cytoplasmic granules within the fibroblasts, but the granules still varied in size and affinity for the stain. Within 3 to 5 days, additional small discrete granules formed and, though these cells appeared similar to normal mast cells, many still maintained their cytoplasmic processes, suggesting their fibroblastic origin. While the surrounding fibroblasts ingest much of the released granular substance and either store or metabolize the material, this fibroblastic function is not considered sufficient to account for all of the material released. The excess may serve to accelerate the inflammatory response to tissue injury. It would appear that the fibroblastic function is protective in nature but is overwhelmed by the widespread spontaneous response of the mast cells to injury. B. S.

The Effects of Adrenocortical Hormones on Albumin Metabolism Studied With Albumin-I^{131}. Rothschild, M. A., Schreiber, S. S., Oratz, M., and McGee, H. L.: J. Clin. Invest. **37**: 1229, 1958.

Rabbit serum albumin labeled with I^{131} was injected intravenously into healthy rabbits. Assay for I^{131} was made on plasma, stool, and urine speci-

mens for from 10 to 14 days, at which point cortisone and antibiotics were administered. The levels of I^{131} were then followed for from 13 to 19 days longer, when a second dose of albumin-I^{131} was administered. A similar experiment was carried out in human beings, using pooled human serum albumin labeled with I^{131}. The serum albumin concentration decreased during adrenal steroid administration. The rate of degradation of albumin was increased by 58 per cent. Synthesis of albumin increased during the cortisone administration period to compensate for 91 per cent of the albumin destruction in rabbits. Human studies showed a 27 per cent increase in degradation of albumin and increased synthesis to replace 48 per cent of the albumin destroyed while corticosteroids were given. Extravascular albumin diminished under hormone therapy and the final deficit in albumin balance "was derived mainly from the extravascular stores, a finding which has also been recorded following the administration of large doses of desiccated thyroid." Adrenal hormones do not exert an antianabolic effect on all protein metabolism, since they stimulate serum albumin synthesis. E. K.

The Clearance of Heterologous Protein From the Circulation of Normal and Immunized Man. Fletcher, A. P., Alkjaersig, N., and Sherry, S.: J. Clin. Invest. **37**: 1306, 1958.

Streptokinase is derived from hemolytic streptococci and, as such, is a ubiquitous antigen to which most of the population has probably had some exposure. The intravenous infusion over a period of minutes to hours of labeled streptokinase into "non-immune" human beings and into those particularly immunized against this substance indicated that there were two clearing rates for streptokinase protein. The fast rate of removal appeared to be related to combination of streptokinase with antibody, whereas the slow rate "was shown to be operative in the absence of plasma antibody and may be due to activity of the reticulo-endothelial system." Unlike rabbits, immunized man forms a soluble nonprecipitating antigen-antibody complex with streptokinase, and this complex is efficiently removed from the circulation. Patients with an initial plasma antibody level below 50,000 units maintained a steady fibrinolysin level when streptokinase was infused at a rate of 35,000 units per hour. Patients with initial plasma levels of from 50,000 to 100,000 units usually required 50,000 units per hour, and if initial levels were still higher 100,000 units per hour might be needed to maintain a relatively steady fibrinolytic state. No allergic reactions were encountered. E. K.

Dynamics of Release of Histamine From Tissue Mast Cell. Smith, D. E.: Science **128**: 207, 1958.

The mast cells of the transilluminated mesentery of the intact, anesthetized rat were studied by microscopic observations and cinephotomicrographic recordings. Observations were made with the mesentery bathed in Tyrode's solution containing Compound 48/80, stilbamidine, protamine sulfate, or toluidine blue. These compounds cause the release of histamine from mast cells. Before exposure to the compounds, these cells appear round or spindle-shaped and densely packed with dark granules. Shortly after exposure to any of the preceding solutions, the granules suddenly lose their dark appearance and become almost invisible. At the same time, the mast cell gradually swells to one and one-third times its original diameter. On exposure to toluidine blue, the mast cell nucleus takes on a blue color when 50 to 80 per cent of the granules have lost their dark appearance. The faded granules then begin to stain purple, and the mast cell shrinks toward its normal size.

The author interprets the changes in the refractile properties of the granules as a manifestation of the freeing of histamine from its binding with heparin, either within or on the surface of the granule. Once the heparin is free, it becomes osmotically active; water enters the cell and causes it to swell. The author further suggests that histamine is freed from the heparin because the histamine liberators have a stronger affinity for heparin than does histamine. It is believed that when the toluidine blue is employed the granules do not stain until binding sites are made available on molecules of heparin. When the toluidine blue molecules bind heparin, the latter becomes osmotically inactive and the cell shrinks. Also, as histamine moves out of the cell, there is further loss of water and shrinkage. Thus, heparin is thought to remain within mast cells treated with histamine liberators. B. S.

Primary Biliary Cirrhosis Showing a High Titer of Autoantibody. Report of a Case. Mackay, I. R.: New England J. Med. **258**: 185, 1958.

Extremely high titers (1:1,000) of complement-fixing antibodies were obtained to a variety of human tissue antigens, notably liver and kidney, in a 38-year-old woman whose liver biopsy specimen showed changes suggestive of active, chronic, biliary cirrhosis. A cholangiogram, performed at laparotomy, showed a normal extrahepatic biliary system. Although treatment with a thyroxin derivative, tri-iodothyroacetate, produced some improvement in the course of the illness (notably a pronounced fall in the serum bilirubin, cholesterol, and lipid levels), there was no change in the complement-fixing antibody titers. Treatment with prednisolone resulted in considerable subjective improvement, with a gain in strength and a moderate fall in the serum total lipid and cholesterol levels. This therapy also effected a transient decrease in the complement-fixing antibody titers. E. W.

Bronchodilators and Corticosteroids in the Treatment of Obstructive Pulmonary Emphysema. Franklin, W., Michaelson, A. L., Lowell, F. C., and Schiller, I. W.: New England J. Med. **258**: 774, 1958.

Obstructive pulmonary emphysema, a chronic progressive process manifested clinically by dyspnea, occurs in middle-aged or elderly men who have had no previous localized or diffuse chronic pulmonary disease. In its advanced form, the outstanding characteristic is striking airway obstruction manifested by a reduction in maximal expiratory flow rate. The disease is frequently preceded by a chronic cough, which develops many years before the onset of obstructive manifestations. The authors state that it can be differentiated from asthma chiefly by the fact that it occurs after the age of 40 and that the obstruction is irreversible, despite the relatively short duration of symptoms. Evidence that heavy cigarette smoking is a common cause of the disease in New England has been presented. Fifty-eight patients were treated for relief of dyspnea with bronchodilators (isopropylarterenol) and were studied by means of the expirogram, a kymographic tracing of forced expiration. Steroid tablets consisting of cortisone 25 mg., cortisol 20 mg., prednisone 5 mg., or prednisolone 5 mg. were administered in a dosage of 8 tablets or more for two to four days, followed by 4 tablets or more daily for one to three weeks, or until maximum improvement had occurred. About one-half of the patients received steroid treatment. "In the entire group, there were 13 patients with peptic ulcer, 6 with congestive heart failure and 1 with both. The pulmonary dysfunction in most cases could be partially corrected by intensive therapy. Combined treatment with bronchodilator drugs and steroids resulted in a mean increase in vital capacity and first-second

volume of almost 50 per cent of the pretreatment value. The subjective improvement was often greater than the change in vital capacity or the maximum expiratory flow rate suggested." E. W.

Side-Effects Noted in Treatment With Methylprednisolone (Medrol). Report of Seventy-seven Consecutive Cases. McMahon, F. G., and Gordon, E. S.: J. A. M. A. **168**: 1208, 1958.

Sixty-seven patients and 10 healthy volunteers were treated with methylprednisolone (Medrol) in a metabolic study of its side effects. The dosage varied between 4 and 32 mg. per day, and therapy was administered for a few days to 7 months. Obesity was noted in 14 patients after doses exceeding 12 mg. per day were given for periods of two or more months. The occurrence of hypertension or changes in electrolyte balance was insignificant. Bloating and dyspepsia occurred in 4 patients, and these symptoms were relieved by antacids. In one patient an old duodenal ulcer became reactivated and was associated with mild hemorrhage. Two subjects with previously proved duodenal ulcers failed to develop any activation of the disease while receiving either 16 or 32 mg. of Medrol daily for weeks. Mild personality changes developed in 5 patients; these were characterized by mood swings, euphoria, insomnia, and increased doctor dependence. There was one instance of a chronic hypercortisone syndrome consisting of increased fatigability, emotional instability, and generalized muscular and joint pains. There was no exacerbation of latent infection or masking of known infection. The authors stress the fact that all patients receiving adequate doses of steroids for maintenance therapy must be considered to have adrenal insufficiency. When major stresses occur, such as trauma, infection, or surgery, an approximate threefold increase in steroid dosage must be employed until the stress has been removed. On discontinuing steroid therapy, a gradual decrease of dosage is mandatory. Preferably, the morning doses are decreased first, since 70 per cent of the endogenous adrenal cortical output of hydrocortisone is believed to occur between midnight and 10 A.M. M. C.

Announcement

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